

BLEOMYCIN - bleomycin injection

Teva Parenteral Medicines, Inc

Package Insert

Rx Only

WARNING

It is recommended that bleomycin for injection, USP, be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Pulmonary fibrosis is the most severe toxicity associated with bleomycin for injection, USP. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and in those receiving greater than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses.

A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin for injection, USP.

DESCRIPTION

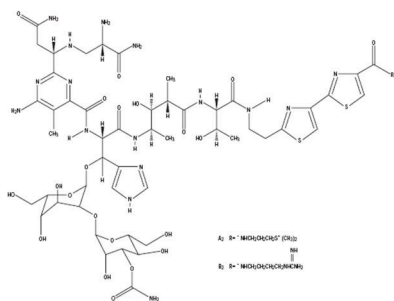
Bleomycin for injection, USP, is a sterile mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*. It is freely soluble in water. Bleomycin for injection, USP contains sterile bleomycin sulfate equivalent to 15 units or 30 units of bleomycin. Sulfuric acid or sodium hydroxide used, if necessary to adjust pH.

Bleomycin for injection may be given by the intramuscular, intravenous or subcutaneous routes.

Bleomycins are a group of related basic glycopeptides which differ in the terminal amine substituent of the common structural unit, bleomycin acid. The main components of bleomycin for injection are bleomycins A₂ and B₂. Chemically, bleomycin A₂ is N₁-[3(dimethylsulfonic) propyl]-bleomycinamide and bleomycin B₂ is N₁-[4-(aminolminomethyl)amino]butyl]-bleomycinamide.

The molecular formula of bleomycin A₂ is C₅₅H₈₄N₁₇O₂₁S₃ and a calculated molecular weight of 1414. The molecular formula of bleomycin B₂ is C₅₅H₈₄N₂₀O₂₁S₂ and a calculated molecular weight of 1425. The structural formula of bleomycins A₂ and B₂ are shown below.

Note: A unit of bleomycin is equal to the formerly used milligram activity. The term milligram activity is a misnomer and was changed to units to be more precise.



CLINICAL PHARMACOLOGY

Although the exact mechanism of action of bleomycin is unknown, available evidence would seem to indicate that the main mode of action is the inhibition of DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis.

In mice, high concentrations of bleomycin are found in the skin, lungs, kidneys, peritoneum, and lymphatics. Tumor cells of the skin and lungs have been found to have high concentrations of bleomycin in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of bleomycin found in bone marrow may be related to high levels of bleomycin degradative enzymes found in that tissue.

In patients with normal renal function, 60% to 70% of an administered dose is recovered in the urine as active bleomycin. In patients with a creatinine clearance of > 35 mL per minute, the serum or plasma terminal elimination half-life of bleomycin is approximately 115 minutes. In patients with a creatinine clearance of < 35 mL per minute, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases. It was reported that patients with moderately severe renal failure excreted less than 20% of the dose in the urine. This result would suggest that severe renal impairment could lead to accumulation of the drug in blood.

Information on the dose proportionality of bleomycin is not available.

When administered intrapleurally for the treatment of malignant pleural effusion, bleomycin acts as a sclerosing agent.

Following intrapleural administration to a limited number of patients (n=4), the resultant bleomycin plasma concentrations suggest a systemic absorption of approximately 45%.

The safety and efficacy of bleomycin 60 units and tetracycline (1 gm) as treatment for malignant pleural effusion were evaluated in a multicenter, randomized trial. Patients were required to have cytologically positive pleural effusion, good performance status (0, 1, 2), lung re-expansion following tube thoracostomy with drainage rates of 100 mL/24 hr. or less, no prior intrapleural therapy, no prior systemic bleomycin therapy, no chest irradiation and no recent change in systemic therapy. Overall survival did not differ between the bleomycin 60 units (n=44) and tetracycline (n=41) groups. Of patients evaluated within 30 days of instillation, the recurrence rate was 36% (10/28) with bleomycin and 67% (18/27) with tetracycline (p=0.023). Toxicity was similar between groups.

INDICATIONS AND USAGE

Bleomycin for injection should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents.

Squamous Cell Carcinoma

Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingivae, epiglottis, skin, larynx), penis, cervix, and vulva. The response to bleomycin is poorer in patients with previously irradiated head and neck cancer.

Lymphomas

Hodgkin's Disease, non-Hodgkin's lymphoma.

Testicular Carcinoma

Embryonal cell, choriocarcinoma, and teratocarcinoma.

Bleomycin has also been shown to be useful in the management of:

Malignant Pleural Effusion

Bleomycin is effective as a sclerosing agent for the treatment of malignant pleural effusion and prevention of recurrent pleural effusions.

CONTRAINDICATIONS

Bleomycin is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

WARNINGS

Patients receiving bleomycin for injection must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function.

Pulmonary toxicities occur in 10% of treated patients. In approximately 1%, the nonspecific pneumonitis induced by bleomycin progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended. (See **ADVERSE REACTIONS-Pulmonary.**)

A severe idiosyncratic reaction (similar to anaphylaxis) consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin. Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses. (See **ADVERSE REACTIONS-Idiosyncratic Reactions.**)

Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported, infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Usage in Pregnancy

Pregnancy Category D

Bleomycin can cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in rats. Administration of intraperitoneal doses of 1.5 mg/kg/day to rats (about 1.6 times the recommended human dose on a unit/m² basis) on days 6-15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. Bleomycin is abortifacient but not teratogenic in rabbits, at i.v. doses of 1.2 mg/kg/day (about 2.4 times the recommended human dose on a unit/m² basis) given on gestation days 6-18.

There have been no studies in pregnant women. If bleomycin is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with bleomycin for injection.

PRECAUTIONS

General

Bleomycin clearance may be reduced in patients with impaired renal function. No guidelines have been established for dose adjustments, but bleomycin should be used with extreme caution in patients with significant renal impairment.

Carcinogenesis, Mutagenesis and Impairment of Fertility

The carcinogenic potential of bleomycin in humans is unknown. A study in F344-type male rats demonstrated an increased incidence of nodular hyperplasia after induced lung carcinogenesis by nitrosamines, followed by treatment with bleomycin. In another study where the drug was administered to rats by subcutaneous injection at 0.35 mg/kg weekly (3.82 units/m² weekly or about 30% at the recommended human dose), necropsy findings included dose related injection site fibrosarcomas as well as various renal tumors. Bleomycin has been shown to be mutagenic both *in vitro* and *in vivo*. The effects of bleomycin on fertility have not been studied.

Pregnancy

Pregnancy Category D. (See **WARNINGS** section.)

Nursing Mothers

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued by women receiving bleomycin for injection therapy.

Pediatric Use

Safety and effectiveness of bleomycin in pediatric patients have not been established.

ADVERSE REACTIONS

Pulmonary

This is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Approximately 1% of patients treated have died of pulmonary fibrosis. Pulmonary toxicity is both dose and age related, being more common in patients over 70 years of age and in those receiving over 400 units total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses. Some published reports have suggested that the risk of pulmonary toxicity may be increased when bleomycin is used in combination with G-CSF (filgrastim) or other cytokines. However, randomized clinical studies completed to date have not demonstrated an increased risk of pulmonary complications in patients treated with bleomycin and G-CSF.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to bleomycin has been extremely difficult. The earliest symptom associated with bleomycin pulmonary toxicity is dyspnea. The earliest sign is fine rales.

Radiographically, bleomycin-induced pneumonitis produces nonspecific patchy opacities, usually of the lower lung fields. The most common changes in pulmonary function tests are a decrease in total lung volume and a decrease in vital capacity. However, these changes are not predictive of the development of pulmonary fibrosis.

The microscopic tissue changes due to bleomycin toxicity include bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous edema, and interstitial fibrosis. The acute stage may involve capillary changes and subsequent fibrinous exudation into alveoli producing a change similar to hyaline membrane formation and progressing to a diffuse interstitial fibrosis resembling the Hamman-Rich syndrome. These microscopic findings are nonspecific; e.g., similar changes are seen in radiation pneumonitis and pneumocystic pneumonitis.

To monitor the onset of pulmonary toxicity, roentgenograms of the chest should be taken every 1 to 2 weeks. If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug related. Recent studies have suggested that sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DL_{CO}) during treatment with bleomycin for injection may be an indicator of subclinical pulmonary toxicity. It is recommended that the DL_{CO} be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus the drug should be discontinued when the DL_{CO} falls below 30% to 35% of the pretreatment value.

Because of bleomycin's sensitization of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered in surgery. While long exposure to very high oxygen concentrations is a known cause of lung damage, after bleomycin administration, lung damage can occur at lower concentrations that are usually considered safe. Suggested preventive measures are:

1. Maintain FIO₂ at concentrations approximating that of room air (25%) during surgery and the postoperative period.
2. Monitor carefully fluid replacement, focusing more on colloid administration rather than crystalloid.

Sudden onset of an acute chest pain syndrome suggestive of pleuropericarditis has been rarely reported during bleomycin for injection infusions. Although each patient must be individually evaluated, further courses of bleomycin for injection do not appear to be contraindicated.

Pulmonary adverse events which may be related to the intrapleural administration of bleomycin have been reported only rarely.

Idiosyncratic Reactions

In approximately 1% of the lymphoma patients treated with bleomycin, an idiosyncratic reaction, similar to anaphylaxis clinically, has been reported. The reaction may be immediate or delayed for several hours, and usually occurs after the first or second dose. It consists of hypotension, mental confusion, fever, chills, and wheezing. Treatment is symptomatic including volume expansion, pressor agents, antihistamines, and corticosteroids.

Integument and Mucous Membranes

These are the most frequent side effects, being reported in approximately 50% of treated patients. These consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperkeratosis, nail changes, alopecia, pruritus, and stomatitis have also been reported. It was necessary to discontinue bleomycin for injection therapy in 2% of treated patients because of these toxicities.

Sclerodema-like skin changes have also been reported as part of postmarketing surveillance.

Skin toxicity is a relatively late manifestation usually developing in the 2nd and 3rd week of treatment after 150 to 200 units of bleomycin have been administered and appears to be related to the cumulative dose.

Intrapleural administration of bleomycin has occasionally been associated with local pain. Hypotension possibly requiring symptomatic treatment has been reported infrequently. Death has been very rarely reported in association with bleomycin pleurodesis in these very seriously ill patients.

Other

Vascular toxicities coincident with the use of bleomycin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS) or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with bleomycin in combination with vinblastine with or without cisplatin or, in a few cases, with bleomycin as a single agent. It is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors. Fever, chills, and vomiting were frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumor site, phlebitis, and other local reactions were reported infrequently. Malaise was also reported as part of postmarketing surveillance.

DOSAGE AND ADMINISTRATION

BECAUSE OF THE POSSIBILITY OF AN ANAPHYLACTOID REACTION, LYMPHOMA PATIENTS SHOULD BE TREATED WITH 2 UNITS OR LESS FOR THE FIRST TWO DOSES. IF NO ACUTE REACTION OCCURS, THEN THE REGULAR DOSAGE SCHEDULE MAY BE FOLLOWED.

The following dose schedule is recommended: **Squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma** - 0.25 to 0.50 units/kg (10 to 20 units/m²) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease - 0.25 to 0.50 units/kg (10 to 20 units/m²) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given. Pulmonary toxicity of bleomycin appears to be dose related with a striking increase when the total dose is over 400 units. Total doses over 400 units should be given with great caution.

Note: When bleomycin for injection is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

Improvement of Hodgkin's Disease and testicular tumors is prompt and noted within 2 weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancers respond more slowly, sometimes requiring as long as 3 weeks before any improvement is noted.

Malignant Pleural Effusion - 60 units administered as a single dose bolus intrapleural injection.

Administration

Bleomycin for injection may be given by the intramuscular, intravenous, or subcutaneous or intrapleural routes.

Intramuscular or Subcutaneous

The bleomycin for injection, USP 15 units vial should be reconstituted and dissolved with 1 to 5 mL of sterile water for injection, USP, sodium chloride injection, 0.9%, USP, or bacteriostatic water for injection, USP. The bleomycin for injection, USP 30 units vial should be reconstituted and dissolved with 2 to 10 mL of the above diluents.

Intravenous

The contents of the 15 units or 30 units vial should be dissolved in 5 mL or more or 10 mL or more, respectively of sodium chloride injection, 0.9%, USP, and administered slowly over a period of 10 minutes

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Intrapleural

60 units of bleomycin is dissolved in 50-100 mL sodium chloride injection 0.9% and administered through a thoracostomy tube following drainage of excess pleural fluid and confirmation of complete lung expansion. The literature suggests that successful pleurodesis is, in part, dependent upon complete drainage of the pleural fluid and reestablishment of negative intrapleural pressure prior to instillation of a sclerosing agent. Therefore, the amount of drainage from the chest tube should be as minimal as possible prior to instillation of bleomycin. Although there is no conclusive evidence to support this contention, it is generally accepted that chest tube drainage should be less than 100 mL in a 24 hour period prior to sclerosis. However, bleomycin instillation may be appropriate when drainage is between 100-300 mL under clinical conditions that necessitate sclerosis therapy. The thoracostomy tube is clamped after bleomycin instillation. The patient is moved from the supine to the left and right lateral positions several times during the next four hours. The clamp is then removed and suction reestablished. The amount of time the chest tube remains in place following sclerosis is dictated by the clinical situation.

The intrapleural injection of topical anesthetics or systemic narcotic analgesia is generally not required.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Stability

The sterile powder is stable under refrigeration 2°-8°C (36°-46°F) and should not be used after the expiration date is reached.

Bleomycin for injection, USP should not be reconstituted or diluted with 5% dextrose injection or other dextrose containing diluents.

When reconstituted in 5% dextrose injection and analyzed by HPLC, bleomycin for injection, USP demonstrates a loss of A₂ and B₂ potency that does not occur when bleomycin for injection, USP is reconstituted in 0.9% sodium chloride injection, USP.

Bleomycin for injection, USP is stable for 24 hours at room temperature in 0.9 % sodium chloride injection.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁷ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Bleomycin for Injection, USP contains sterile bleomycin sulfate equivalent to 15 units or 30 units of bleomycin. Bleomycin for Injection, USP is supplied as follows:

NDC Number

0703 3154-01	15 Units per Vial	Individually packaged
0703 3155-01	30 Units per Vial	Individually packaged

Store dry powder under refrigeration 2°-8°C (36°-46°F).

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA* 1985; 253(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians* 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), *Am J Health-Syst Pharm*, 1996; 53:1669-1685.

Issued: July 2007

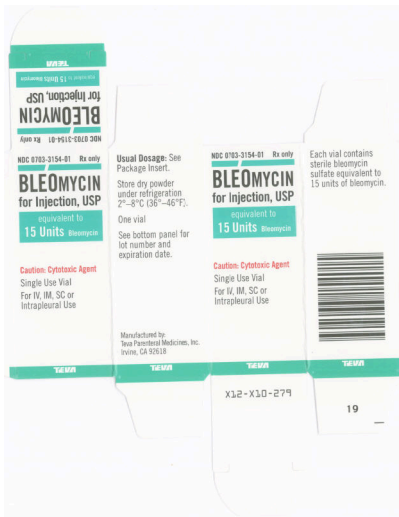
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Teva Parenteral Medicines, Inc.,

Irvine, CA 92618

PRINCIPAL DISPLAY PANEL - 15 UNIT CARTON
NDC 0703-3154-01

Rx only
BLEOMYCIN
for Injection, USP
equivalent to
15 Units Bleomycin
Caution: Cytotoxic Agent
Single Use Vial
For IV, IM, SC or
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TEVA



PRINCIPAL DISPLAY PANEL - 30 UNIT CARTON
NDC 0703-3155-01

Rx only
BLEOMYCIN
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30 Units Bleomycin
Caution: Cytotoxic Agent
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